REMARKS

Status of the Claims

Claims 31 – 47 are pending, with claims 37 and 41 being independent. Without conceding the propriety of the rejections, claims 31, 32, 34, and 36 have been amended to even more clearly recite and distinctly claim the present invention. New claims 37 – 47 have been added. Support for the claim amendments and new claims may be found throughout the specification; therefore, no new matter has been added.

Claims 24 – 30 have been cancelled without prejudice to or disclaimer of the subject matter contained therein as drawn to non-elected subject matter. Applicants expressly reserve the right to file a divisional application directed to the subject matter of these claims.

The specification has also been amended to correct two typographical errors contained therein.

Applicants respectfully request the Examiner to reconsider and withdraw the outstanding rejections in view of the foregoing amendments and the following remarks.

Restriction/Election Requirement

Applicants would like to thank the Examiner for indicating that it is likely that the subgenera of G3 and G4, and thus Group 5 (claims 31-36 drawn to a method of treating an inflammatory condition, limited to G3) and Group 6 (claims 31-36 drawn to a method of treating an inflammatory condition, limited to G4), may be rejoined.

Applicants maintain their previous traversal as set forth in their April 11, 2002 Reply. Specifically, Applicants maintain that generic claim 31 covers species in addition to those recited in claims 34 – 36 and respectfully request that the original restriction requirement be recast to contain a group directed to claims 31 – 36, drawn to a method of treating an inflammatory condition.

Rejections under 35 U.S.C. §112, First Paragraph

Claims 31-36 have been rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification as to enable one skilled in the art to which it pertains to make and/or use the invention. Without conceding

the propriety of the rejection, claims 31, 32, 34, and 36 have been amended and new claims 37 – 47 have been added. Applicants respectfully traverse this rejection.

The presently claimed invention is related to methods of treating a disorder, involving binding of alpha-9 integrin to an alpha-9 integrin ligand, in a mammalian subject comprising administering to a mammalian subject in need thereof a pharmaceutically effective dosage of an alpha-9 integrin antagonist compound. In the presently claimed methods, the disorder may be an inflammatory condition.

The present specification teaches that it has been discovered that alpha-9 integrins are involved in inflammatory responses, and thus, alpha-9/beta-1 integrin modulatory compounds may be used in methods of treating disorders involving the binding of alpha-9 integrin to an alpha-9 integrin ligand, including inflammatory conditions. The present specification further teaches that in studies it has been found that, despite their sequence and ligand binding site dissimilarities, alpha-4/beta-1 integrin and alpha-9 integrin share similar binding sites for small molecules, and that binding to such sites serves to similarly modulate their abilities to bind to endogenous ligands. (page 12). Accordingly, compounds that modulate binding of alpha-4/beta-1 integrin to any of its ligands are good candidates for modulating binding of alpha-9 integrin to its ligand(s). (pages 13- 14).

The specification teaches that assays and test systems for determining whether a test compound is active in binding to and modulating activity of alpha-4/beta-1 integrin are well known in the art and thus compounds can be first screened for alpha-4/beta-1 integrin activity. (pages 16 – 19). The specification teaches that "[w]hile absolute inhibitory concentration values may vary from assay to assay and operator to operator, compounds that inhibit (or enhance) activity at a concentration no higher than about 1 mM, and preferably no higher than about 100 μm should be considered as candidates for alph-9 integrin modulatory agents." (page 19). Accordingly, the specification further teaches compounds identified as exhibiting alpha-4/beta-1 integrin activity can then be tested for alpha-9 integrin activity. The specification provides exemplary assays for measuring alpha-9 integrin binding and activity. (pages 19 – 21 and Example 2).

The specification teaches that "[g]enerally, it is appreciated that useful drugs will be active in vitro or in vivo at concentrations less than about 100 μm and preferably less than

about 20 μm." (page 21). Example 1 merely teaches that each of the compounds as described in Examples 1 – 373 of parent application USSN 08/904,424 exhibited IC_{50}s of 15 μm or less; however, the example does not set a requirement that the compounds exhibit this IC_{50}.

Accordingly, Applicants respectfully submit that the specification more than adequately describes the invention in such terms as to enable a person skilled in the art to make and use the invention. The specification provides considerable guidance to enable a skilled artisan to make, test, and use an alpha-9 integrin antagonist to treat a disorder involving binding of alpha-9 integrin to an alpha-9 integrin ligand, including inflammatory conditions. Under 35 U.S.C. § 112, first paragraph, the test of enablement is not whether any experimentation is necessary, but whether it is undue, and case law clearly states that "a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). In addition, there is no requirement that all the compounds used in the claimed methods have the same profile or degree of activity. See, for example, *Ex parte Cole et al.* 223 U.S.P.Q. 94, 95 (Board of Patent Appeals and Interferences, 1984).

Therefore, Applicants respectfully request that the rejections under 35 U.S.C. § 112, First Paragraph be withdrawn.

Rejection under 35 U.S.C. §112, Second Paragraph

Claims 31 – 36 have been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Without conceding the propriety of the rejection, claims 31, 32, 34, and 36 have been amended and new claims 37 – 47 have been added. Accordingly, Applicants respectfully traverse this rejection.

In particular, claims 31 – 36 have been rejected as indefinite as to the intended inflammatory condition. The presently claimed methods recite that the disorder to be treated involves binding of alpha-9 integrin to an alpha-9 integrin ligand, and this disorder can be an inflammatory condition. Therefore, inflammatory conditions to be treated by the methods of the presently claimed invention are those involving binding of alpha-9 integrin to an alpha-9

integrin ligand. Accordingly, Applicants respectfully submit that this rejection has been obviated.

Claim 31 has been rejected as indefinite due to the recitation of the phrase "pharmaceutically effective." Applicants respectfully submit that the phrase "pharmaceutically effective" has been clearly defined. The specification teaches that appropriate dosages and dosage schedules are determine in accordance with the condition being treated, and a number of variables, including, but not limited to the intended mode of administration, the pharmacokinetics of the active compound, and the size of the subject. (page 27 – 28). The specification further teaches the amount administered to the patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. Accordingly, the "pharmaceutically effective dosage" means the amount or dosage of compound that, when administered to a mammal for treating a disorder, is sufficient to effect such treatment. Also as taught in the specification, this amount will depend on the disease condition being treated, as well as the judgment of the attending clinician depending upon factors such as the severity of the inflammation, the age, weight and general condition of the patient, and the like. (page 28). Accordingly, Applicants respectfully submit that the phrase "pharmaceutically effective dosage" is clearly defined.

Claim 31 has been rejected as indefinite due to the process steps and endpoint. Without conceding the propriety of the rejection, claim 31 has been amended and new claims 37 - 47 have been added. Accordingly, Applicants respectfully submit that this rejection has been obviated.

Claim 32 has been rejected as indefinite due to the phrase "neutrophil adhesion." Without conceding the propriety of the rejection, claim 32 has been amended to recite "neutrophil activity." Applicants respectfully submit that it is well know to those of skill in the art that when activated, neutrophils phagocytose and destroy "foreign" bodies, thus playing an important role in inflammation. Accordingly, Applicants respectfully submit that this rejection has been obviated.

Claim 36 has been rejected for the typographical error in reciting "4-methylpiperzin-1-". Applicants have amended Claims 34 and 36 to correct the typographical error so that

they recite "-4-methylpiperazin-1-". Accordingly, Applicants respectfully submit that this rejection has been obviated.

In view of the above, Applicants respectfully request that the rejections under 35 U.S.C. § 112, Second Paragraph be withdrawn.

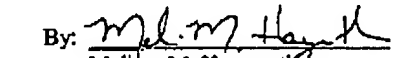
Conclusion

Without conceding the propriety of the rejections, claims 31, 32, 34, and 36 have been amended and new claims 37-47 have been added, as provided above, to even more clearly recite and distinctly claim Applicants' invention and to pursue an early allowance.

In view of the foregoing remarks, reconsideration of the claims and allowance of the subject application is earnestly solicited. The Examiner is invited to contact the undersigned at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: 
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Mark-up of Specification

Marked-up Paragraph on page 4, lines 8-13

--In preferred embodiments, pharmaceutical compositions and methods of treatment of the invention employ alpha-9 antagonist compounds that inhibit binding between alpha-9 integrin and an alpha-9 integrin ligand. Preferred ligands in this regard include any ligand found to specifically bind to alpha-9 integrin, as exemplified by osteopontin, tenascin, and VCAM-1. Due to its association with inflammatory reactions, [V-CAM-1] VCAM-1 is particular preferred for a test compound in this regard.--

Marked-up Paragraph beginning on page 22, line 26

--Alpha-9 integrin modulatory compounds identified and selected in accordance with the present invention find use in a number of disorders associated with alpha-9 integrin activity. Particularly, in view of discoveries described herein with respect to the neutrophil localization of alpha-9 integrin, as well as its ability to interact with VCAM-1, it is appreciated that alpha-9 integrin inhibitory compounds will find particular utility in the treatment of a variety of disorders which include an inflammatory component, particularly those to which the inflammatory component is associated with [VLA-4] VCAM-1 binding to alpha-9 integrin.--

Mark-up of Claims

31. (Amended) [A] The method of Claim 37, wherein the disorder is [treating] an inflammatory condition [in mammalian subject, comprising administering to the subject a pharmaceutically effective dosage of an alpha-9 integrin antagonist compound].

32. (Amended) The method of Claim 31, wherein said inflammatory condition is characterized by increased neutrophil activity [adhesion].

34. (Amended) The method of Claim 31, wherein said alpha-9 integrin antagonist compound exhibits a potency in inhibiting binding between alpha-9 integrin and an alpha-9 integrin ligand that is at least 1/1000 as high as an inhibitory potency exhibited by a compound selected from the group consisting of:

[N-(toluene-4-sulfonyl)-L-prolyl-L-4(4-methylpiperzin-1-ylcarbonyloxy)phenylalanine] N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

N-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl-)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-N-methyl-L-alaninyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-[(1,1-dioxo)thiamorpholin-3-carbonyl]-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(N-*p*-toluenesulfonyl)prolyl-4-(piperazinoyloxy)phenylalanine,

N-(N-*p*-toluenesulfonyl)sarcosyl-4-(N,N-dimethylcarbamyloxy)phenylalanine, and

N-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-[3-(N,N-dimethyl)propoxy]phenylalanine.

36. (Amended) The method of Claim 31, wherein said alpha-9 integrin antagonist is selected from the group consisting of:

[N-(toluene-4-sulfonyl)-L-prolyl-L-4(4-methylpiperzin-1-ylcarbonyloxy)phenylalanine] N-(toluene-4-sulfonyl)-L-prolyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-prolyl-L-4(N,N-dimethylcarbamyloxy)phenylalanine,

N-(1-methylpyrazole-4-sulfonyl)-L-prolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl-)-L-(1,1-dioxo-5,5-dimethyl)thiaprolyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-N-methyl-L-alaninyl-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(toluene-4-sulfonyl)-L-[(1,1-dioxo)thiamorpholin-3-carbonyl]-L-4-(N,N-dimethylcarbamyloxy)phenylalanine,

N-(N-*p*-toluenesulfonyl)prolyl-4-(piperazinoyloxy)phenylalanine,

N-(N-*p*-toluenesulfonyl)sarcosyl-4-(N,N-dimethylcarbamyloxy)phenylalanine, and

N-(toluene-4-sulfonyl)-L-(5,5-dimethyl)thiaprolyl-L-4-[3-(N,N-dimethyl)propoxy]phenylalanine.